```
=> d his

     (FILE 'HOME' ENTERED AT 17:36:12 ON 17 NOV 2001)

     FILE 'REGISTRY' ENTERED AT 17:37:44 ON 17 NOV 2001
               E METABOTROPIC GLUTAMATE RECEPTOR/CN
               E METABOTROPIC GLUTAMATE RECEPTOR 5/CN
               E MGLUR5/CN

     FILE 'CAPLUS' ENTERED AT 17:41:33 ON 17 NOV 2001
L1           114 S MGLUR5 (P)(ANTAGONIST OR INHIBIT?)
L2            11 S L1 AND (ANXIETY OR ANXIOUS? OR PAIN OR ANALGES? OR ?NOCICEPT?

     FILE 'STNGUIDE' ENTERED AT 17:51:40 ON 17 NOV 2001
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=> s mglur5 (p)(antagonist or inhibit?)
           339 MGLUR5
        120230 ANTAGONIST
       1423650 INHIBIT?
L1         114 MGLUR5 (P)(ANTAGONIST OR INHIBIT?)

=> s l1 and (anxiety or anxious? or pain or analges? or ?nocicept? or anxiolyt?)
          7713 ANXIETY
           329 ANXIOUS?
         22829 PAIN
         45216 ANALGES?
         11465 ?NOCICEPT?
          6728 ANXIOLYT?
L2           11 L1 AND (ANXIETY OR ANXIOUS? OR PAIN OR ANALGES? OR ?NOCICEPT?
              OR ANXIOLYT?)

=> d l2 abs ibib kwic 1-11

L2   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2001 ACS
AB   Glutamate receptors play an essential role in fear-related learning and
     memory.  The present study was designed to assess the role of the group I
     metabotropic glutamate receptor (mGluR) subtype 5 in the acquisition and
     retrieval of conditioned fear in rats.  The selective mGluR5
     antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) was applied
     systemically (0.0, 0.3, 3.0, 30.0 mg/kg per os) 60 min before the
     acquisition training and before the expression of conditioned fear, resp.,
     in the fear-potentiated startle paradigm.  MPEP dose-dependently blocked
     the acquisition of fear.  This effect was not due to state-dependent
     learning.  MPEP also prevented the expression of fear at a dose of 30.0
     mg/kg.  As a pos. control for these effects, the authors showed that the
     benzodiazepine anxiolytic compd. diazepam (1.25 mg/kg i.p.) also
     blocked acquisition and expression of fear potentiated startle.  MPEP did
     not affect the baseline startle magnitude, short-term habituation of
     startle, sensitization of startle by footshocks or prepulse
     inhibition of startle.  These data indicate a crucial role for
     mGluR5 in the regulation of fear conditioning.  In the highest
     dose MPEP might exert anxiolytic properties.
ACCESSION NUMBER:         2001:502705  CAPLUS
DOCUMENT NUMBER:          135:236855
TITLE:                    The metabotropic glutamate receptor antagonist
                          2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks fear
                          conditioning in rats
AUTHOR(S):                Schulz, B.; Fendt, M.; Gasparini, F.; Lingenhohl, K.;
                          Kuhn, R.; Koch, M.
CORPORATE SOURCE:         Animal Physiology, University of Tubingen, Tubingen,
                          Germany
SOURCE:                   Neuropharmacology (2001), 41(1), 1-7
                          CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER:                Elsevier Science Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          35
REFERENCE(S):             (1) Anwyl, R; Brain Research Reviews 1999, V29, P83
                              CAPLUS
                          (2) Bordi, F; Neuropharmacology 1996, V35, P1557
                              CAPLUS
                          (4) Davis, M; Behavioural Brain Research 1993, V58,
```

P175 CAPLUS
(6) Davis, M; Psychopharmacology 1979, V62, P1 CAPLUS
(7) Fendt, M; Brain Research 1994, V661, P163 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Glutamate receptors play an essential role in fear-related learning and memory. The present study was designed to assess the role of the group I metabotropic glutamate receptor (mGluR) subtype 5 in the acquisition and retrieval of conditioned fear in rats. The selective **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)-pyridine (MPEP) was applied systemically (0.0, 0.3, 3.0, 30.0 mg/kg per os) 60 min before the acquisition training and before the expression of conditioned fear, resp., in the fear-potentiated startle paradigm. MPEP dose-dependently blocked the acquisition of fear. This effect was not due to state-dependent learning. MPEP also prevented the expression of fear at a dose of 30.0 mg/kg. As a pos. control for these effects, the authors showed that the benzodiazepine **anxiolytic** compd. diazepam (1.25 mg/kg i.p.) also blocked acquisition and expression of fear potentiated startle. MPEP did not affect the baseline startle magnitude, short-term habituation of startle, sensitization of startle by footshocks or prepulse **inhibition** of startle. These data indicate a crucial role for **mGluR5** in the regulation of fear conditioning. In the highest dose MPEP might exert **anxiolytic** properties.

IT **Anxiolytics**
Learning
(metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine MPEP blocks fear conditioning in rats)

IT Glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metabotropic, **mGluR5**; metabotropic glutamate receptor **antagonist** 2-methyl-6-(phenylethynyl)-pyridine MPEP blocks fear conditioning in rats)

L2 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2001 ACS

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and antagonists for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, **pain**, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent antagonists of **mGluR5**. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive **mGluR5 antagonist**. Studies using these agents have yielded data to support the involvement of **mGluR5** in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or against representative NMDA, AMPA, and kainate receptors up to concns. of 100 .mu.M. The compd., administered orally (100 mg/kg) produced a 70% reversal of mech. hyperalgesia in the Freund's complete adjuvant model of inflammatory **pain**. By Oct. 1999, investigations with SIB-1757 and SIB-1893 had been discontinued in favor of MPEP.

ACCESSION NUMBER: 2000:903884 CAPLUS
DOCUMENT NUMBER: 135:13755
TITLE: Methylphenylethynylpyridine (MPEP)(Novartis)

AUTHOR(S): Micheli, Fabrizio
CORPORATE SOURCE: Glaxo Wellcome Medicines Research Centre, Verona, 37135, Italy
SOURCE: Curr. Opin. Invest. Drugs (PharmaPress Ltd.) (2000), 1(3), 355-359
CODEN: COIDAZ
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 66
REFERENCE(S): (1) Allgeier, H; WO 00020001 1999 CAPLUS
(14) Bordi, F; Brain Res 2000, V871(2), P223 CAPLUS
(18) Chapman, A; Neuropharmacology 2000, V39(9), P1567 CAPLUS
(25) Gasparini, F; Bioorg Med Chem Lett 2000, V10(11), P1241 CAPLUS
(28) Gasparini, F; Neuropharmacology 1999, V38(10), P1493 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and antagonists for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, **pain**, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent antagonists of **mGluR5**. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive **mGluR5 antagonist**. Studies using these agents have yielded data to support the involvement of **mGluR5** in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or against representative NMDA, AMPA, and kainate receptors up to concns. of 100 .mu.M. The compd., administered orally (100 mg/kg) produced a 70% reversal of mech. hyperalgesia in the Freund's complete adjuvant model of inflammatory **pain**. By Oct. 1999, investigations with SIB-1757 and SIB-1893 had been discontinued in favor of MPEP.

ST review MPEP antiischemic **analgesic** anticonvulsant NMDA antagonist

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AMPA-binding, antagonist; MPEP in treatment of epilepsy, stroke, **anxiety**, **pain**, and neurodegenerative disease)

IT **Analgesics**
Anti-ischemic agents
Anticonvulsants
Anxiolytics
(MPEP in treatment of epilepsy, stroke, **anxiety**, **pain**, and neurodegenerative disease)

IT Glutamate antagonists
(NMDA antagonists; MPEP in treatment of epilepsy, stroke, **anxiety**, **pain**, and neurodegenerative disease)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(metabotropic, **mGluR5**, **antagonist**; MPEP in treatment of epilepsy, stroke, **anxiety**, **pain**, and neurodegenerative disease)

IT 96206-92-7, MPEP
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MPEP in treatment of epilepsy, stroke, **anxiety**, **pain**, and neurodegenerative disease)

L2 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2001 ACS

AB Recently, selective and systemically active antagonists for the metabotropic glutamate 5 receptor (mGlu5) were discovered, and the most potent deriv. was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety**-dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the no. of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the no. of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1, 10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ACCESSION NUMBER: 2000:846141 CAPLUS
DOCUMENT NUMBER: 134:36966
TITLE: **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents
AUTHOR(S): Spooren, Will P. J. M.; Vassout, Annick; Neijt, Hans C.; Kuhn, Rainer; Gasparini, Fabrizio; Roux, Silvain; Porsolt, Roger D.; Gentsch, Conrad
CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, Basel, Switz.
SOURCE: J. Pharmacol. Exp. Ther. (2000), 295(3), 1267-1275
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 28
REFERENCE(S):
(2) Broekkamp, C; Eur J Pharmacol 1986, V126, P223 CAPLUS
(3) Chesselet, M; Trends Neurosci 1996, V19, P417 CAPLUS
(4) Conn, P; Ann Rev Pharmacol Toxicol 1997, V37, P205 CAPLUS
(6) Davidson, A; Psychopharmacologia 1969, V15, P159

CAPLUS
(7) Duncan, G; Brain Res 1996, V713, P79 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents

AB Recently, selective and systemically active antagonists for the metabotropic glutamate 5 receptor (mGlu5) were discovered, and the most potent deriv. was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety** -dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the no. of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the no. of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1, 10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ST methylphenylethynylpyridine **mGluR5 antagonist** **anxiolytic**

IT Behavior
(locomotor; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

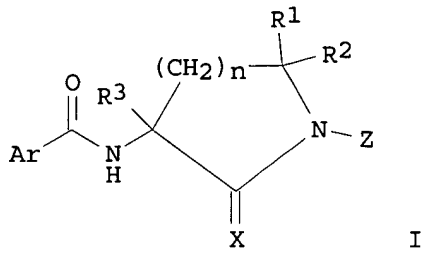
IT **Anxiolytics**
Psychotomimetics
(**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **mGluR5**; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

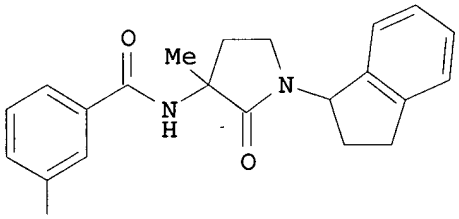
IT Mental activity
(sedation; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

L2 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2001 ACS
GI



I



II

AB The title compds. (I) [wherein n = 0-2; X = O, S, NH, or NOH; R1 and R2 = independently H, CN, CO2R, CONHR, alkyl, or tetrazole; or R1 and R2 together = :O; R = H or alkyl; R3 = (cyclo)alkyl, alkenyl, CH2OH, alkoxymethyl, or CO2H; Ar = (un)substituted (hetero)arom. group; Z = (un)substituted indanyl, indenyl, phenylalkyl, phenylcyclopropyl, or CH2BHet; B = CHR, CR2, alkyl, CO, CHOH, CH2O, CH:CH, CH2CO, CH2S, CH2S(O), CH2SO2, CHCO2R, or CHNR2; Het = heterocycle] were prepd. by conventional and soln. phase combinatorial methods for the treatment or prevention of a physiol. disorder assocd. with an excess of stimulation of the human Group I metabotropic glutamate receptors, esp. those designated as **mGluR5**. Examples include syntheses and phys. data for approx. 140 compds., description of bioassays with data summaries, and 8 pharmaceutical formulations employing I. Thus, (R,R)-II was prepd. by reductive amination of N-(3-bromobenzoyl)-.alpha.-(2-oxoethyl)alanine (prepn. given) with R-(-)-1-aminoindane in the presence of NaBH4 in MeOH followed by spontaneous cyclization to the lactam. When **mGluR5** expressing cell lines were used, representative compds. of the invention generated IC50 values of .ltoreq. 30 .mu.M in a phosphoinositide assay and resulted in .gtoreq. 70% **inhibition** at concns. of 30 .mu.M in a calcium flux assay. I are useful in the treatment of neurodegenerative conditions and **pain** (no data).

ACCESSION NUMBER: 2000:824216 CAPLUS
DOCUMENT NUMBER: 134:4857
TITLE: Preparation of 3-acylamino-3-methylpyrrolidin-2-ones and analogs as metabotropic glutamate receptor antagonists
INVENTOR(S): Clark, Barry Peter; Cwi, Cynthia Lynn; Harris, John Richard; Kingston, Ann Elizabeth; Scott, William Leonard
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 103 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069816	A1	20001123	WO 2000-US8223	20000517

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-134410 P 19990517
OTHER SOURCE(S): MARPAT 134:4857
REFERENCE COUNT: 7
REFERENCE(S):
(1) Clark, B; WO 0026198 A 2000 CAPLUS
(2) Favaron, M; CAPLUS
(3) Favaron, M; NEUROREPORT 1993, V4(7), P967 CAPLUS
(4) Kozikowski, A; CAPLUS
(5) Kozikowski, A; J MED CHEM 1993, V36(18), P2706 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The title compds. (I) [wherein n = 0-2; X = O, S, NH, or NOH; R1 and R2 = independently H, CN, CO2R, CONHR, alkyl, or tetrazole; or R1 and R2 together = :O; R = H or alkyl; R3 = (cyclo)alkyl, alkenyl, CH2OH, alkoxymethyl, or CO2H; Ar = (un)substituted (hetero)arom. group; Z = (un)substituted indanyl, indenyl, phenylalkyl, phenylcyclopropyl, or CH2BHet; B = CHR, CR2, alkyl, CO, CHOH, CH2O, CH:CH, CH2CO, CH2S, CH2S(O), CH2SO2, CHCO2R, or CHNR2; Het = heterocycle] were prepd. by conventional and soln. phase combinatorial methods for the treatment or prevention of a physiol. disorder assocd. with an excess of stimulation of the human Group I metabotropic glutamate receptors, esp. those designated as **mGluR5**. Examples include syntheses and phys. data for approx. 140 compds., description of bioassays with data summaries, and 8 pharmaceutical formulations employing I. Thus, (R,R)-II was prepd. by reductive amination of N-(3-bromobenzoyl)-.alpha.-(2-oxoethyl)alanine (prepn. given) with R-(-)-1-aminoindane in the presence of NaBH4 in MeOH followed by spontaneous cyclization to the lactam. When **mGluR5** expressing cell lines were used, representative compds. of the invention generated IC50 values of .ltoreq. 30 .mu.M in a phosphoinositide assay and resulted in .gtoreq. 70% **inhibition** at concns. of 30 .mu.M in a calcium flux assay. I are useful in the treatment of neurodegenerative conditions and **pain** (no data).

ST acylamino pyrrolidinone prepn metabotropic glutamate receptor **mGluR5 antagonist**; pyrrolidinone acylamino prepn neurodegenerative disease treatment **analgesic**

IT **Analgesics**
Combinatorial library
Glutamate antagonists
(prepn. of 3-acylamino-3-methylpyrrolidin-2-ones and analogs by conventional and soln. phase combinatorial methods as metabotropic glutamate receptor antagonists)

L2 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2001 ACS

AB Recent studies suggest a role of Group 1 metabotropic glutamate receptors in mediating the development of spinal hypersensitivity in some **pain** states. Here, the possible role of **mGluR5** receptors in exptl. neuropathic **pain** elicited by ligation of spinal nerves (L5/L6 spinal nerve ligation, SNL) was explored with SIB-1757, a selective **mGluR5 antagonist**. SNL-induced tactile allodynia was detected by decreased paw withdrawal thresholds to probing with von Frey filaments and thermal hyperalgesia by decreased paw withdrawal latencies to radiant heat applied to the plantar aspect of the hindpaw. SIB-1757 was given by either intrathecal (i.th.), s.c. or intraplantar (i.pl.) injection. In SNL rats, i.th. SIB-1757 produced a partial reversal of tactile allodynia with a shallow dose-response curve ranging over three-orders of magnitude; SIB-1757 was inactive against allodynia when given systemically. SIB-1757 produced full reversal of thermal hyperalgesia in SNL rats following administration either spinally or locally to the injured paw; administration to the contralateral paw had no effect. SIB-1757 did not produce **antinociception** in either the SNL or sham-operated rats by any route. These data suggest a significant modulation of thermal hyperalgesia by **mGluR5** antagonists, consistent with reports that this receptor may be assocd. with afferent C-fibers. The less impressive effect seen on tactile allodynia, likely to be mediated by large fiber input, suggests that the obsd. modulation may be related to blockade of **mGluR5**-mediated spinal sensitization. These results do not support the involvement of these receptors in modulation of acute **nociception** but suggest the possibility of a role for Group I mGluRs in the mediation of aspects of neuropathic **pain** which may be assocd. with C-fiber inputs.

ACCESSION NUMBER: 2000:661721 CAPLUS
DOCUMENT NUMBER: 134:13274
TITLE: Peripheral and spinal antihyperalgesic activity of SIB-1757, a metabotropic glutamate receptor (**mGLUR5**) **antagonist**, in experimental neuropathic **pain** in rats
AUTHOR(S): Dogrul, A.; Ossipov, M. H.; Lai, J.; Malan, T. P.; Porreca, F.
CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology, Gulhane Medical Military Academy, Ankara, Turk.
SOURCE: Neurosci. Lett. (2000), 292(2), 115-118
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 27
REFERENCE(S): (1) Al-Ghoul, W; Brain Res Bull 1993, V30, P453 CAPLUS
(4) Berthele, A; Dev Brain Res 1999, V112, P39 CAPLUS
(6) Fisher, K; NeuroReport 1998, V9, P1169 CAPLUS
(7) Fisher, K; Pain 1996, V68, P255 CAPLUS
(8) Fisher, K; Pain 1998, V77, P59 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Peripheral and spinal antihyperalgesic activity of SIB-1757, a metabotropic glutamate receptor (**mGLUR5**) **antagonist**, in experimental neuropathic **pain** in rats

AB Recent studies suggest a role of Group 1 metabotropic glutamate receptors in mediating the development of spinal hypersensitivity in some **pain** states. Here, the possible role of **mGluR5** receptors in exptl. neuropathic **pain** elicited by ligation of

spinal nerves (L5/L6 spinal nerve ligation, SNL) was explored with SIB-1757, a selective **mGluR5 antagonist**. SNL-induced tactile allodynia was detected by decreased paw withdrawal thresholds to probing with von Frey filaments and thermal hyperalgesia by decreased paw withdrawal latencies to radiant heat applied to the plantar aspect of the hindpaw. SIB-1757 was given by either intrathecal (i.th.), s.c. or intraplantar (i.pl.) injection. In SNL rats, i.th. SIB-1757 produced a partial reversal of tactile allodynia with a shallow dose-response curve ranging over three-orders of magnitude; SIB-1757 was inactive against allodynia when given systemically. SIB-1757 produced full reversal of thermal hyperalgesia in SNL rats following administration either spinally or locally to the injured paw; administration to the contralateral paw had no effect. SIB-1757 did not produce **antinociception** in either the SNL or sham-operated rats by any route. These data suggest a significant modulation of thermal hyperalgesia by **mGluR5** antagonists, consistent with reports that this receptor may be assocd. with afferent C-fibers. The less impressive effect seen on tactile allodynia, likely to be mediated by large fiber input, suggests that the obsd. modulation may be related to blockade of **mGluR5**-mediated spinal sensitization. These results do not support the involvement of these receptors in modulation of acute **nociception** but suggest the possibility of a role for Group I mGluRs in the mediation of aspects of neuropathic **pain** which may be assocd. with C-fiber inputs.

ST peripheral spinal **analgesia mGluR5 antagonist** SIB1757

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **mGluR5**; peripheral and spinal **analgesic** action of **mGluR5 antagonist** SIB-1757)

IT Nerve, disease
(neuralgia; peripheral and spinal **analgesic** action of **mGluR5 antagonist** SIB-1757)

IT **Analgesics**
(peripheral and spinal **analgesic** action of **mGluR5 antagonist** SIB-1757)

IT **Analgesia**
(spinal; peripheral and spinal **analgesic** action of **mGluR5 antagonist** SIB-1757)

IT 31993-01-8, SIB-1757
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peripheral and spinal **analgesic** action of **mGluR5 antagonist** SIB-1757)

L2 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2001 ACS

AB The effect of the **mGluR5 antagonist**, MPEP (2-Methyl-6-(phenylethynyl)-pyridine), and of the mGluR1 **antagonist**, AIDA((RS)-1-Aminoindan-1,5-dicarboxylic acid), were examd. on **nociceptive** neurons in the ventroposterolateral (VPL) nucleus of the thalamus in response to pressure stimuli to the contralateral hindpaw of rats under urethane anesthesia. I.v. (i.v.) injection of MPEP (0.1, 1, and 10 mg/kg) blocked responses to noxious stimulation in a dose-dependent and reversible manner. AIDA (3 and 15 mg/kg, i.v.), in contrast, had no effect on these cells. MPEP action was selective to noxious stimulation because even when tested at the highest dose (10 mg/kg, i.v.) it did not alter the responses of non-**nociceptive** neurons to brush stimulation. To investigate the site

of action of MPEP, intra-thalamic injections were made during electrophysiol. recordings. Using this method, the **mGluR5 antagonist** did not affect **nociceptive** responses, suggesting that thalamic receptors were not involved in this action. On the other hand, the NMDA thalamic receptors seem to be involved because the NMDA receptor **antagonist**, MK801, successfully blocked responses to noxious pressure stimulation following intra-thalamic injections. In the spinal cord in vitro model, MPEP (30 .mu.M, 60 min) was also able to attenuate ventral root potentials after single shock elec. stimulation of the dorsal root and **inhibit** wind-up response evoked by repetitive stimulation. Taken together, these findings suggest that blockade of the **mGluR5**, but not mGluR1 decreases **nociceptive** transmission in the thalamus and that these effects may be mediated by spinal cord receptors.

ACCESSION NUMBER: 2000:490357 CAPLUS
DOCUMENT NUMBER: 133:188305
TITLE: Involvement of mGluR5 on acute **nociceptive** transmission
AUTHOR(S): Bordi, F.; Ugolini, A.
CORPORATE SOURCE: Pharmacology Department, GlaxoWellcome Medicine Research Centre, Verona, 37100, Italy
SOURCE: Brain Res. (2000), 871(2), 223-233
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 53
REFERENCE(S): (2) Benoist, J; Pain 1983, V15, P333 CAPLUS
(5) Bordi, F; Pain 2000, V84, P213 CAPLUS
(6) Bordi, F; Prog Neurobiol 1999, V59, P55 CAPLUS
(7) Boxall, S; Neuroscience 1996, V74, P13 CAPLUS
(8) Christoffersen, G; Behav Brain Res 1999, V101, P215 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Involvement of mGluR5 on acute **nociceptive** transmission

AB The effect of the **mGluR5 antagonist**, MPEP (2-Methyl-6-(phenylethynyl)-pyridine), and of the mGluR1 **antagonist**, AIDA((RS)-1-Aminoindan-1,5-dicarboxylic acid), were examd. on **nociceptive** neurons in the ventroposterolateral (VPL) nucleus of the thalamus in response to pressure stimuli to the contralateral hindpaw of rats under urethane anesthesia. I.v. (i.v.) injection of MPEP (0.1, 1, and 10 mg/kg) blocked responses to noxious stimulation in a dose-dependent and reversible manner. AIDA (3 and 15 mg/kg, i.v.), in contrast, had no effect on these cells. MPEP action was selective to noxious stimulation because even when tested at the highest dose (10 mg/kg, i.v.) it did not alter the responses of non-**nociceptive** neurons to brush stimulation. To investigate the site of action of MPEP, intra-thalamic injections were made during electrophysiol. recordings. Using this method, the **mGluR5 antagonist** did not affect **nociceptive** responses, suggesting that thalamic receptors were not involved in this action. On the other hand, the NMDA thalamic receptors seem to be involved because the NMDA receptor **antagonist**, MK801, successfully blocked responses to noxious pressure stimulation following intra-thalamic injections. In the spinal cord in vitro model, MPEP (30 .mu.M, 60 min) was also able to attenuate ventral root potentials after single shock elec. stimulation of the dorsal root and **inhibit** wind-up response evoked by repetitive stimulation. Taken together, these findings

suggest that blockade of the **mGluR5**, but not mGluR1 decreases **nociceptive** transmission in the thalamus and that these effects may be mediated by spinal cord receptors.

ST mGluR5 **nociceptive** transmission thalamus

IT Glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(NMDA-binding; involvement of glutamate receptors in acute **nociceptive** transmission)

IT Spinal cord
(blockade of the mGluR5 decreases **nociceptive** transmission in the thalamus and these effects may be mediated by spinal cord receptors)

IT **Pain**
(involvement of mGluR5 in acute **nociceptive** transmission in the ventroposterolateral nucleus)

IT Glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metabotropic, mGluR1; involvement of glutamate receptors in acute **nociceptive** transmission)

IT Glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metabotropic, mGluR5; involvement of mGluR5 in acute **nociceptive** transmission in the ventroposterolateral nucleus)

IT Brain
(thalamus; involvement of mGluR5 in acute **nociceptive** transmission in the ventroposterolateral nucleus)

L2 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2001 ACS

AB The invention provides the use of selective mGluR5 antagonists for the treatment of **pain** and **anxiety**, and the use of mGluR antagonists for the treatment of **pain** in which the **analgesic** effect is achieved by interaction of the antagonists primarily or predominantly at peripheral mGluR receptors.

ACCESSION NUMBER: 2000:240944 CAPLUS
DOCUMENT NUMBER: 132:246378
TITLE: mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**
INVENTOR(S): Allgeier, Hans; Cosford, Nicholas David; Flor, Peter Josef; Gasparini, Fabrizio; Gentsch, Conrad; Hess, Stephen D.; Johnson, Edwin Carl; Kuhn, Rainer; Tricklebank, Mark; Urban, Laszlo; Varney, Mark Andrew; Velicelebi, Gonul; Walker, Katharine
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.; Sibia Neurosciences Inc.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020001	A1	20000413	WO 1999-EP7239	19990930

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG,

MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9961984	A1	20000426	AU 1999-61984	19990930	
BR 9914215	A	20010703	BR 1999-14215	19990930	
EP 1117403	A1	20010725	EP 1999-948905	19990930	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
NO 2001001440	A	20010515	NO 2001-1440	20010321	

PRIORITY APPLN. INFO.:

GB 1998-21503	A	19981002
US 1998-220813	A	19981223
WO 1999-EP7239	W	19990930

OTHER SOURCE(S): MARPAT 132:246378
REFERENCE COUNT: 9
REFERENCE(S):
(1) Bowes, M; BRITISH JOURNAL OF PHARMACOLOGY, MEETING OF THE BRITISH PHARMACOLOGICAL SOCIETY 1999, V126(PROC SUPPL), P250P
(2) Fundytus, M; NEUROREPORT 1998, V9(4), P731 CAPLUS
(4) KnOpfel, T; J MED CHEM 1995, V38(9), P1417 MEDLINE
(5) Mori, M; AGRICULTURAL AND BIOLOGICAL CHEMISTRY V46(1), P309 CAPLUS
(9) Varney, M; JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1999, V290(1), P170 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**

AB The invention provides the use of selective mGluR5 antagonists for the treatment of **pain** and **anxiety**, and the use of mGluR antagonists for the treatment of **pain** in which the **analgesic** effect is achieved by interaction of the antagonists primarily or predominantly at peripheral mGluR receptors.

ST **mGluR5** metabotropic glutamate receptor **antagonist** **pain**; **anxiety** **mGluR5** metabotropic glutamate receptor **antagonist**

IT Nervous system
(central; mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**)

IT Inflammation
(inflammatory **pain**; mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**)

IT **Analgesics**
Anxiolytics
Biological transport
Blood-brain barrier
Drug delivery systems
(mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabotropic, mGluR5; mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(metabotropic, peripheral; mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**)

IT Nerve, disease
(neuropathy, neuropathic **pain**; mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**)

IT Drug delivery systems
(transdermal; mGluR5 metabotropic glutamate receptor antagonists for the treatment of **pain** and **anxiety**)

L2 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2001 ACS

AB G-protein coupled metabotropic glutamate receptors (mGluRs) are important modulators of synaptic transmission in the mammalian CNS and have been implicated in various forms of neuroplasticity and nervous system disorders. Increasing evidence also suggests an involvement of mGluRs in **nociception** and **pain** behavior although the contribution of individual mGluR subtypes is not yet clear. Subtypes mGluR1 and **mGluR5** are classified as group I mGluRs and share the ability to stimulate phosphoinositide hydrolysis and activate protein kinase C. The present study examd. the role of group I mGluRs in **nociceptive** processing and capsaicin-induced central sensitization of primate spinothalamic tract (STT) cells in vivo. In 10 anesthetized male monkeys (Macaca fascicularis) extracellular recordings were made from 20 STT cells in the lumbar dorsal horn. Responses to brief (15 s) cutaneous stimuli of innocuous (BRUSH) and barely and substantially noxious (PRESS and PINCH, resp.) intensity were recorded before, during, and after the infusion of group I mGluR agonists and antagonists into the dorsal horn by microdialysis. Cumulative concn.-response relationships were obtained by applying different concns. for at least 20 min each (at 5 .mu.L/min). The actual concns. reached in the tissue are 2-3 orders of magnitude lower than those in the microdialysis fibers (values in this paper refer to the latter). The group I antagonists were also applied at 10-25 min after capsaicin injection. S-DHPG, a group I agonist at both mGluR1 and **mGluR5**, potentiated the responses to innocuous and noxious stimuli (BRUSH > PRESS > PINCH) at low concns. (10-100 .mu.M) but had **inhibitory** effects at higher concns. (1-10 mM). The **mGluR5** agonist CHPG (1 .mu.M-100 mM) did not potentiate but **inhibited** all responses (10-100 mM). AIDA (1 .mu.M-100 mM), a mGluR1-selective **antagonist**, dose-dependently depressed the responses to PINCH and PRESS but not to BRUSH. The group I (mGluR1 > **mGluR5**) **antagonist** CPCCOEt (1 .mu.M-100 mM) had similar effects. Intradermal injections of capsaicin sensitized the STT cells to cutaneous mech. stimuli. The enhancement of the responses by capsaicin resembled the potentiation by the group I mGluR agonist S-DHPG (BRUSH > PRESS > PINCH). CPCCOEt (1 mM) reversed the capsaicin-induced sensitization when given as posttreatment. After washout of CPCCOEt, the sensitization resumed. Similarly, AIDA (1 mM) reversed the capsaicin-induced sensitization and also blocked the potentiation by S-DHPG. These data suggest that the mGluR1 subtype is activated endogenously during brief high-intensity cutaneous stimuli (PRESS, PINCH) and is critically involved in capsaicin-induced central sensitization.

ACCESSION NUMBER: 1999:496994 CAPLUS
DOCUMENT NUMBER: 131:295791
TITLE: Role of metabotropic glutamate receptor subtype mGluR1 in brief **nociception** and central sensitization of primate STT cells
AUTHOR(S): Neugebauer, Volker; Chen, Ping-Sun; Willis, William D.

CORPORATE SOURCE: Department of Anatomy and Neurosciences and Marine Biomedical Institute, The University of Texas Medical Branch, Galveston, TX, 77555-1069, USA
SOURCE: J. Neurophysiol. (1999), 82(1), 272-282
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 58
REFERENCE(S): (1) Aniksztejn, L; Eur J Pharmacol 1991, V205, P327 CAPLUS
(2) Aronica, E; J Neurosci 1997, V17, P8588 CAPLUS
(3) Aronica, E; Mol Pharmacol 1993, V44, P981 CAPLUS
(5) Bleakman, D; Mol Pharmacol 1992, V42, P192 CAPLUS
(6) Bond, A; Neuropharmacology 1995, V34, P1015 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Role of metabotropic glutamate receptor subtype mGluR1 in brief **nociception** and central sensitization of primate STT cells

AB G-protein coupled metabotropic glutamate receptors (mGluRs) are important modulators of synaptic transmission in the mammalian CNS and have been implicated in various forms of neuroplasticity and nervous system disorders. Increasing evidence also suggests an involvement of mGluRs in **nociception** and **pain** behavior although the contribution of individual mGluR subtypes is not yet clear. Subtypes mGluR1 and **mGluR5** are classified as group I mGluRs and share the ability to stimulate phosphoinositide hydrolysis and activate protein kinase C. The present study examd. the role of group I mGluRs in **nociceptive** processing and capsaicin-induced central sensitization of primate spinothalamic tract (STT) cells in vivo. In 10 anesthetized male monkeys (Macaca fascicularis) extracellular recordings were made from 20 STT cells in the lumbar dorsal horn. Responses to brief (15 s) cutaneous stimuli of innocuous (BRUSH) and barely and substantially noxious (PRESS and PINCH, resp.) intensity were recorded before, during, and after the infusion of group I mGluR agonists and antagonists into the dorsal horn by microdialysis. Cumulative concn.-response relationships were obtained by applying different concns. for at least 20 min each (at 5 .mu.L/min). The actual concns. reached in the tissue are 2-3 orders of magnitude lower than those in the microdialysis fibers (values in this paper refer to the latter). The group I antagonists were also applied at 10-25 min after capsaicin injection. S-DHPG, a group I agonist at both mGluR1 and **mGluR5**, potentiated the responses to innocuous and noxious stimuli (BRUSH > PRESS > PINCH) at low concns. (10-100 .mu.M) but had **inhibitory** effects at higher concns. (1-10 mM). The **mGluR5** agonist CHPG (1 .mu.M-100 mM) did not potentiate but **inhibited** all responses (10-100 mM). AIDA (1 .mu.M-100 mM), a mGluR1-selective **antagonist**, dose-dependently depressed the responses to PINCH and PRESS but not to BRUSH. The group I (mGluR1 > **mGluR5**) **antagonist** CPCCOEt (1 .mu.M-100 mM) had similar effects. Intradermal injections of capsaicin sensitized the STT cells to cutaneous mech. stimuli. The enhancement of the responses by capsaicin resembled the potentiation by the group I mGluR agonist S-DHPG (BRUSH > PRESS > PINCH). CPCCOEt (1 mM) reversed the capsaicin-induced sensitization when given as posttreatment. After washout of CPCCOEt, the sensitization resumed. Similarly, AIDA (1 mM) reversed the capsaicin-induced sensitization and also blocked the potentiation by S-DHPG. These data suggest that the mGluR1 subtype is activated endogenously during brief high-intensity cutaneous stimuli (PRESS, PINCH) and is critically involved in capsaicin-induced central sensitization.

ST mGluR1 **nociception** sensitization primate spinothalamic tract cell

IT Spinal cord
(dorsal horn; mGluR1 role in **nociception** and central sensitization of primate spinothalamic tract cells)

IT Macaca fascicularis
Pain
(mGluR1 role in **nociception** and central sensitization of primate spinothalamic tract cells)

IT Glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metabotropic, mGluR1; mGluR1 role in **nociception** and central sensitization of primate spinothalamic tract cells)

IT Nervous system
(spinothalamic tract; mGluR1 role in **nociception** and central sensitization of primate spinothalamic tract cells)

IT 404-86-4 162870-29-3, S-3,5-Dihydroxyphenylglycine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(mGluR1 role in **nociception** and central sensitization of primate spinothalamic tract cells)

L2 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2001 ACS

AB A combined study of behavioral and electrophysiol. tests was carried out to assess the role of metabotropic glutamate receptors (mGluRs) in mediating sensory inputs to the spinal cord of the rat. In the behavioral study the responses of conscious animals, with or without carrageenan-induced inflammation, to noxious mech. and thermal stimuli were obsd. both before and after the intrathecal administration of mGluR antagonists l(+)-2-amino-3-phosphonopropionic acid (l-AP3) and (S)-4-carboxy-3-hydroxyphenylglycine (CHPG). It was found that the mGluR **antagonist** (S)-CHPG was capable of increasing both mech. threshold and thermal latency in both groups of animals, and l-AP3 did so in those with inflammation induced in their hindpaw. Following this study, the responses of single lamina III-V dorsal horn neurons to an innocuous A.beta. fiber brush stimulus and a noxious C fiber (mustard oil) stimulus were extracellularly recorded and the effect of ionophoretically applied drugs was examd. Cyclothiazide (CTZ), a selective **antagonist** at mGluR1, markedly reduced the activity evoked by mustard oil, but not that elicited by brushing of the receptive field. Activity induced in dorsal horn neurons by ionophoresing various mGluR subgroup agonists was examd. CTZ successfully **inhibited** the activity evoked by group I mGluR agonist 3,5-dihydroxyphenylglycine (DHPG). In comparison to the neurons which responded to the ionophoresis of DHPG, less were activated by the selective **mGluR5** agonist transazetidine dicarboxylic acid (t-ADA). Together these results indicate that group I mGlu receptors, in particular mGluR1, play a crucial role in mediating **nociception**, particularly following a sustained noxious input.

ACCESSION NUMBER: 1997:780474 CAPLUS
DOCUMENT NUMBER: 128:111064
TITLE: Behavioral and electrophysiological evidence supporting a role for group I metabotropic glutamate receptors in the mediation of **nociceptive** inputs to the rat spinal cord
AUTHOR(S): Young, Marie R.; Fleetwood-Walker, Susan M.; Dickinson, Tracey; Blackburn-Munro, Gordon; Sparrow, Helen; Birch, Phil J.; Bountra, Chas
CORPORATE SOURCE: Summerhall, Royal (Dick) School of Veterinary Studies,

Department of Preclinical Veterinary Sciences,
University of Edinburgh, Edinburgh EH9 1QH, UK
SOURCE: Brain Res. (1997), 777(1,2), 161-169
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Behavioral and electrophysiological evidence supporting a role for group I metabotropic glutamate receptors in the mediation of **nociceptive** inputs to the rat spinal cord

AB A combined study of behavioral and electrophysiol. tests was carried out to assess the role of metabotropic glutamate receptors (mGluRs) in mediating sensory inputs to the spinal cord of the rat. In the behavioral study the responses of conscious animals, with or without carrageenan-induced inflammation, to noxious mech. and thermal stimuli were obsd. both before and after the intrathecal administration of mGluR antagonists 1(+)-2-amino-3-phosphonopropionic acid (1-AP3) and (S)-4-carboxy-3-hydroxyphenylglycine (CHPG). It was found that the mGluR **antagonist** (S)-CHPG was capable of increasing both mech. threshold and thermal latency in both groups of animals, and 1-AP3 did so in those with inflammation induced in their hindpaw. Following this study, the responses of single lamina III-V dorsal horn neurons to an innocuous A.beta. fiber brush stimulus and a noxious C fiber (mustard oil) stimulus were extracellularly recorded and the effect of ionophoretically applied drugs was examd. Cyclothiazide (CTZ), a selective **antagonist** at mGluR1, markedly reduced the activity evoked by mustard oil, but not that elicited by brushing of the receptive field. Activity induced in dorsal horn neurons by ionophoresing various mGluR subgroup agonists was examd. CTZ successfully **inhibited** the activity evoked by group I mGluR agonist 3,5-dihydroxyphenylglycine (DHPG). In comparison to the neurons which responded to the ionophoresis of DHPG, less were activated by the selective **mGluR5** agonist transazetidine dicarboxylic acid (t-ADA). Together these results indicate that group I mGlu receptors, in particular mGluR1, play a crucial role in mediating **nociception**, particularly following a sustained noxious input.

ST metabotropic glutamate receptor **nociceptive** neurotransmission spinal

IT Nerves
(A.beta. fiber; behavioral and electrophysiol. evidence for group I metabotropic glutamate receptors involvement in mediation of **nociceptive** inputs to spinal cord)

IT C-fiber (nerve)
Dorsal horn (spinal cord)
Inflammation
Neurotransmission
Pain
Spinal cord
(behavioral and electrophysiol. evidence for group I metabotropic glutamate receptors involvement in mediation of **nociceptive** inputs to spinal cord)

IT mGluR1 (receptor)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(behavioral and electrophysiol. evidence for group I metabotropic glutamate receptors involvement in mediation of **nociceptive** inputs to spinal cord)

IT Metabotropic glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(group I; behavioral and electrophysiol. evidence for group I

metabotropic glutamate receptors involvement in mediation of **nociceptive** inputs to spinal cord)

L2 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2001 ACS

AB The present study examd. the mGluR subtypes involved in (1S,3R)-ACPD-induced spontaneous **nociceptive** behaviors (SNB) by administering the following selective agonists by the intrathecal (i.t.) route: (RS)-DHPG, trans-ADA (Group I; mGluR1/5 and **mGluR5**, resp.), (1S,3S)-ACPD, (2R,4R)-APDC (Group II), and L-AP4 (Group III). (RS)-DHPG administration induced SNB that were of significantly greater intensity and longer duration than those induced by an equal dose of (1S,3R)-ACPD. No other agonists produced SNB, except (1S,3S)-ACPD, which may be attributable to a nonselective action at mGluR1. Intrathecal treatment with the mGluR **antagonist** (+)-MCPG or the NMDA **antagonist** D-AP5 prior to (RS)-DHPG administration dose-dependently reduced SNB. It is suggested that a possible interaction between NMDA and mGluR1 is a crit. event in the maintenance of persistent **nociception**.

ACCESSION NUMBER: 1997:171605 CAPLUS
DOCUMENT NUMBER: 126:207730
TITLE: Comparison of **nociceptive** effects produced by intrathecal administration of mGluR agonists
AUTHOR(S): Fisher, Kim; Coderre, Terence J.
CORPORATE SOURCE: Pain Mechanisms Laboratory, Clinical Research Institute of Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: NeuroReport (1996), 7(15-17), 2743-2747
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Comparison of **nociceptive** effects produced by intrathecal administration of mGluR agonists

AB The present study examd. the mGluR subtypes involved in (1S,3R)-ACPD-induced spontaneous **nociceptive** behaviors (SNB) by administering the following selective agonists by the intrathecal (i.t.) route: (RS)-DHPG, trans-ADA (Group I; mGluR1/5 and **mGluR5**, resp.), (1S,3S)-ACPD, (2R,4R)-APDC (Group II), and L-AP4 (Group III). (RS)-DHPG administration induced SNB that were of significantly greater intensity and longer duration than those induced by an equal dose of (1S,3R)-ACPD. No other agonists produced SNB, except (1S,3S)-ACPD, which may be attributable to a nonselective action at mGluR1. Intrathecal treatment with the mGluR **antagonist** (+)-MCPG or the NMDA **antagonist** D-AP5 prior to (RS)-DHPG administration dose-dependently reduced SNB. It is suggested that a possible interaction between NMDA and mGluR1 is a crit. event in the maintenance of persistent **nociception**.

ST mGluR receptor agonist spinal cord **pain**

IT **Pain**
Spinal cord
(**nociceptive** effects produced by intrathecal administration of mGluR agonists)

IT mGluR1 (receptor)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**nociceptive** effects produced by intrathecal administration of mGluR agonists)

IT 111900-32-4
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(**nociceptive** effects produced by intrathecal administration of mGluR agonists)

IT 6384-92-5, NMDA
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**nociceptive** effects produced by intrathecal administration of mGluR agonists)

L2 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2001 ACS
AB The present study examd. the role of mGluRs in **nociceptive** responses of male Long-Evans rats following a s.c. injection of 1% (30 .mu.l) or 2.5% (50 .mu.l) formalin to the plantar surface of the hindpaw. Intrathecal (i.t.) administration of the mGluR4/mGluR6-mGluR8 agonist, L(+)-2-amino-4-phosphonobutyric acid (L-AP4), the mGluR1/**mGluR5** antagonists, (S)-4-carboxyphenylglycine ((S)-4CPG) or (S)-4-carboxy-3-hydroxyphenylglycine ((S)-4C3HPG), but not the non-selective **antagonist**, (+)-.alpha.-methyl-4-carboxyphenylglycine ((+)-MCPG), to the lumbar spinal cord slightly reduced second phase **nociceptive** responses. An i.t. injection of the mGluR1/**mGluR5** agonist, (RS)-3,5-dihydroxyphenylglycine ((RS)-DHPG) or the mGluR2/mGluR3 agonist, (1S,3S)-1-aminocyclopentane-1,3-dicarboxylic acid ((1S,3S)-ACPD), but not (2S,1'R,2'R,3'R)-2-(2'3'-dicarboxy-cyclopropyl)-glycine (DCG-IV), dose-dependently enhanced formalin-induced **nociception** in the second phase. In addn., the facilitation of **nociceptive** responses induced by (1S,3S)-ACPD or (RS)=DHPG was reduced by prior i.t. administration of the mGluR antagonists, (+)-MCPG ro (S)-4C3HPG, resp., as well as by the N-MethylD-aspartate (NMDA) receptor **antagonist**, D(-)-2-amino-5-phosphonopentanoic acid (D-AP5). These results indicate that although mGluRs may play a minor role in formalin-induced **nociception**, mGluR agonist-related facilitation of formalin scores may reflect an interaction with the NMDA receptor.

ACCESSION NUMBER: 1997:99290 CAPLUS
DOCUMENT NUMBER: 126:166764
TITLE: The contribution of metabotropic glutamate receptors (mGluRs) to formalin-induced **nociception**
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TI The contribution of metabotropic glutamate receptors (mGluRs) to formalin-induced **nociception**
AB The present study examd. the role of mGluRs in **nociceptive** responses of male Long-Evans rats following a s.c. injection of 1% (30 .mu.l) or 2.5% (50 .mu.l) formalin to the plantar surface of the hindpaw. Intrathecal (i.t.) administration of the mGluR4/mGluR6-mGluR8 agonist, L(+)-2-amino-4-phosphonobutyric acid (L-AP4), the mGluR1/**mGluR5** antagonists, (S)-4-carboxyphenylglycine ((S)-4CPG) or (S)-4-carboxy-3-hydroxyphenylglycine ((S)-4C3HPG), but not the non-selective **antagonist**, (+)-.alpha.-methyl-4-carboxyphenylglycine ((+)-MCPG), to the lumbar spinal cord slightly reduced second phase **nociceptive** responses. An i.t. injection of the mGluR1/**mGluR5** agonist, (RS)-3,5-dihydroxyphenylglycine ((RS)-DHPG) or the mGluR2/mGluR3 agonist, (1S,3S)-1-aminocyclopentane-1,3-dicarboxylic acid ((1S,3S)-ACPD), but not (2S,1'R,2'R,3'R)-2-(2'3'-dicarboxy-cyclopropyl)-

glycine (DCG-IV), dose-dependently enhanced formalin-induced **nociception** in the second phase. In addn., the facilitation of **nociceptive** responses induced by (1S,3S)-ACPD or (RS)=DHPG was reduced by prior i.t. administration of the mGluR antagonists, (+)-MCPG ro (S)-4C3HPG, resp., as well as by the N-MethylD-aspartate (NMDA) receptor **antagonist**, D(-)-2-amino-5-phosphonopentanoic acid (D-AP5). These results indicate that although mGluRs may play a minor role in formalin-induced **nociception**, mGluR agonist-related facilitation of formalin scores may reflect an interaction with the NMDA receptor.

ST metabotropic glutamate receptor **nociception**

IT **Pain**
(contribution of metabotropic glutamate receptors to formalin-induced **nociception** in rats)

IT NMDA receptors
mGluR1 (receptor)
mGluR2 (receptor)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(contribution of metabotropic glutamate receptors to formalin-induced **nociception** in rats)

IT Metabotropic glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(mGluR3; contribution of metabotropic glutamate receptors to formalin-induced **nociception** in rats)

IT Metabotropic glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(mGluR4; contribution of metabotropic glutamate receptors to formalin-induced **nociception** in rats)

IT Receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(mGluR5 (metabotropic glutamatergic receptor 5); contribution of metabotropic glutamate receptors to formalin-induced **nociception** in rats)

IT Metabotropic glutamate receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(mGluR6; contribution of metabotropic glutamate receptors to formalin-induced **nociception** in rats)

IT Receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(mGluR8 (metabotropic glutamatergic receptor 8)mGluR8; contribution of metabotropic glutamate receptors to formalin-induced **nociception** in rats)